

Mechanisms in Choroid Plexus Epithelial Development

Grant Award Details

Mechanisms in Choroid Plexus Epithelial Development

Grant Type: New Faculty II

Grant Number: RN2-00915

Project Objective: examining how choroid plexus (CP) mechanism is developed as a potential source of stem cells.
 PI is looking at the following aims:
 determine whether Fgf8 is a CPE competency factor
 determine whether Lhx2 suppresses CPE fate
 generate human CPECs

Investigator:

Name: Edwin Monuki
Institution: University of California, Irvine
Type: PI

Disease Focus: Neurological Disorders

Human Stem Cell Use: Embryonic Stem Cell

Award Value: \$2,793,395

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period:	Year 4
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Grant Application Details

Application Title: Mechanisms in Choroid Plexus Epithelial Development

Public Abstract: Buried deep inside the brain are cells known as choroid plexus epithelial (CPe) cells. Although not as famous as other cells in the nervous system, CPe cells perform a large number of important jobs that keep the brain and spinal cord healthy. They produce the fluid (known as cerebrospinal fluid, or CSF) that bathes the brain and spinal cord with many nourishing chemicals, which promote normal nervous system health and function, learning and memory, and neural repair following injury. In addition, CPe cells protect the brain and spinal cord from toxins – such as heavy metals and the amyloid-beta peptide associated with Alzheimer's disease – by absorbing them or preventing them from entering the nervous system altogether by forming the so-called blood-CSF barrier. Accordingly, as CPe functions diminish during normal aging or in accelerated fashion in certain diseases, memory loss, Alzheimer's disease, and a number of other neurologic and neuropsychiatric disorders may ensue or become worse. The ability to grow and make CPe cells should therefore enable many clinical applications, such as CPe cell replacements, transplants, and pharmaceutical studies to identify beneficial drugs that can pass through the blood-CSF barrier. However, all of these potential applications are limited by the current inability to make and expand CPe cells in culture. Our published and preliminary studies suggest that it should be feasible to generate CPe cells in culture. Our broad goals are to study how CPe cells form during normal development, then use this information to make human CPe cells for clinical applications. To achieve this goal, our approach will be to use mice to study how the CPe develops normally, then use both mouse and human stem cells to make CPe cells in culture. Our published and preliminary studies have defined one critical factor for this process (known as Bmp4) and identify candidate factors that work with Bmp4 to regulate whether or not CPe cells are formed. In Aim 1, we test whether a molecule known as Fgf8 provides CPe "competency" – i.e. whether Fgf8 allows cells to become CPe cells when exposed to Bmp4. In Aim 2, we test whether a gene known as Lhx2 prevents cortical cells from becoming CPe cells in response to Bmp4. In Aim 3, we manipulate Bmp4, Fgf8, and Lhx2 in hESC cultures to make human CPe cells. If successful, this proposal should greatly improve our understanding of normal CPe development and enable a number of CPe-based clinical applications with significant potential to improve human health.

Statement of Benefit to California: Our proposal to study choroid plexus epithelial (CPe) cell development and to make CPe cells in culture for clinical applications should benefit the State of California and its citizens in a number of ways. In the short term, this project will provide employment, education and training in stem cell research for a handful of California residents, and will support California-based companies that provide supplies for the stem cell and biomedical research communities. In the longer term, success in making CPe cells in culture should enable many new CPe-based clinical applications, stimulate CPe studies and applications by stem cell companies, and enable screens to identify agents that allow for passage of therapeutics across the blood-CSF barrier, which remains a significant roadblock to the development of pharmaceuticals for neurological and neuropsychiatric disorders. Such outcomes would ultimately stimulate investment in California-based companies and benefit the health of many California citizens, which may reduce the economic burden of health care in the state.

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